N-Aralkyl Substitution of 2-Amino-5,6- and -6,7-dihydroxy-1,2,3,4-tetrahydronaphthalenes. 1. Cardiac and Pressor/Depressor Activities

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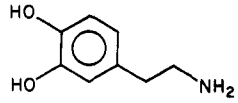
Amino substitution of rigid forms of dopamine [2-amino-5,6-dihydroxy-1,2,3,4-tetrahydronaphthalene (A-5,6-DTN) and 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (A-6,7-DTN)] with aralkyl functionalities was carried out to investigate the role of such structural modifications upon cardiac inotropic/chronotropic and blood pressure activity. Derivatives of A-5,6-DTN were strong vasodepressor agents devoid of inotropic selectivity. Analogues of A-6,7-DTN tended to be vasopressor agents, although strong depressor action was associated with the dihydroxyphenyl-1-methylethyl derivative, which was also an inotropic selective compound. The amino substituent of dobutamine was ineffective in reducing peripheral vascular action when combined with the rigid forms of dopamine. It was also ineffective in imparting inotropic selectivity when combined with A-5,6-DTN. An analysis of these observations in light of existing structure–activity relationships of aminoaralkyl substitution of other catecholamine structures is presented.

Dopamine, 1, has been shown to be an inotropic selective



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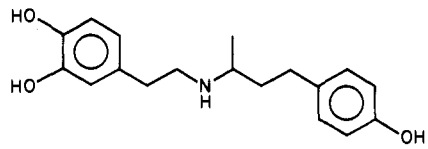
cardiac stimulant; i.e., dopamine is more potent in augmenting the force than the rate of cardiac contraction.[1,2] Present evidence suggests that selective action is due to the preferential release of norepinephrine by dopamine from nerves located in the ventricular myocardium. Any release of norepinephrine from nerves located in the SA node or direct stimulation of SA node β receptors occurs at much higher doses.[1] Selective inotropic activity is also obtained with an *N*-aralkyl derivative of dopamine (dobutamine),[2] **2**. With this compound, however, selectivity



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is thought to be totally due to preferential interaction with postsynaptic β receptors in ventricular myocardium.[2] Dobutamine also possesses minimal peripheral vascular adrenergic receptor activity.[2,3]

In general, it has been possible to differentially modulate the inotropic, chronotropic, and pressor activities of β-agonists possessing the dopamine nucleus via N-substitution with various aralkyl functionalities.[2] In an effort to extend the SAR of these systems, we have synthesized a number of *N*-aralkyl derivatives of A-5,6-DTN and A-6,7-DTN (2-amino-5,6- and -6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene). For comparative purposes, the parent compounds, i.e., A-5,6-DTN and A-6,7-DTN, along with their *N*-isopropyl derivatives were also synthesized and tested.

The ADTN nuclei were chosen because they represent relatively rigid analogues of dopamine, the catecholamine nucleus upon which a great deal of the existing SAR for *N*-aralkyl substitutions is based.[2] The purpose of the present study was threefold: (1) to ascertain if the pattern of activity previously observed with *N*-aralkyl substitution of dopamine can be enhanced with compounds containing a rigid form of dopamine as the catecholamine nucleus, (2) to determine if there is a pharmacological preference for the α or β rotameric forms (i.e., A-5,6-DTN or A-6,7-DTN, respectively) of N-substituted dopamine compounds at β receptors, and (3) to compare the profile of cardiac activity of the unsubstituted 5,6- and 6,7-dihydroxytetralinamines with that of dopamine itself.

Chemistry. The alkyl- and aralkyl-substituted ADTN compounds were prepared by the reductive amination method of Borch[4] using the ADTN with the hydroxy groups protected as methyl ethers and the corresponding ketone or aldehyde. All of the compounds were unstable in aqueous solution over a few hours; however, the compounds were stable for several hours in aqueous bisulfite solution.

Pharmacological Results in Vitro (Table I). The isopropyl derivatives of A-6,7-DTN and A-5,6-DTN, **5** and **12**, were used as standards for comparison with the aralkyl derivatives, since the unsubstituted ADTNs, **4** and **11**, possess a considerable degree of indirect-sympathomimetic activity (see below). In isolated cardiac tissues, **5** and **12** were approximately five orders of magnitude less potent than isoproterenol, **3**. However, in agreement with previous results obtained with the vascular smooth-muscle β receptor,[6] the α rotameric form, **12**, showed relatively greater potency on cardiac tissue than the β rotameric form, **5**. In general, aralkyl substitution resulted in a considerable improvement in cardiac potency over the isopropyl derivatives. Specifically, compounds possessing a catechol substituent, **6**, **7**, **9**, and **13**, showed the greatest potency. A methyl group on the α carbon of the substit-

(1) R. J. Gorczynski, W. G. Anderson, P. W. Erhardt, and D. M. Stout, *J. Pharmacol. Exp. Ther.*, **210**, 252 (1979).
(2) R. R. Tuttle and J. Mills, *Circ. Res.*, **36**, 185 (1975).
(3) S. F. Vatner, R. J. McRitchie, and E. Braunwald, *J. Clin. Invest.*, **53**, 1265 (1974).
(4) R. Borch, M. Bernstein, and H. Durst, *J. Am. Chem. Soc.*, **93**, 2897 (1971).
(5) K. Itoh, M. Motohashi, H. Kuriki, H. Sugihara, N. Inatomi, M. Nishikawa, and Y. Oka, *Chem. Pharm. Bull.*, **25**, 2917 (1977).
(6) L. I. Goldberg, J. D. Kohli, A. N. Kotake, and P. H. Volkman, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **37**, 2396 (1978).

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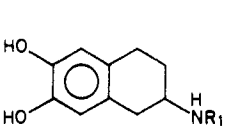
Table I. Potency (EC_{50}) and Relative Intrinsic Activity of Various Aminoaralkyl Derivatives of A-5,6-DTN and A-6,7-DTN in Guinea Pig Isolated Right and Left Atria



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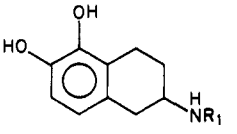

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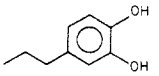
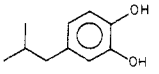
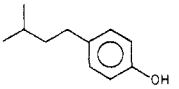
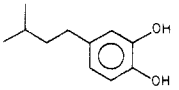
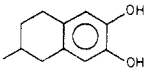
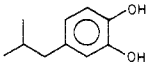
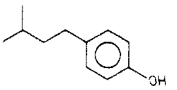
compd	R_1	right atria (rate) $EC_{50} \times 10^{-6}$, M	RIA	n	left atria (force) $EC_{50} \times 10^{-6}$, M	RIA	n
1 (dopamine)		1.5 ± 0.5[b]	1.00 ± 0.05[a]	4	1.7 ± 0.4	1.15 ± 0.038	8
2 (dobutamine)		0.47 ± 0.09	0.90 ± 0.03	7	0.15 ± 0.04	1.12 ± 0.05	8
3 (isoproterenol)		0.0062 ± 0.0004	1.00	55	0.0032 ± 0.0002	1.00	54
4 (A-6,7-DTN)	H	33 ± 5	0.61 ± 0.02	11	2.5 ± 0.8	1.06 ± 0.03	4
5		200 ± 100[c]	0.24 ± 0.03	3	49 ± 19	0.78 ± 0.11	3
6		16 (13, 18)[d]	0.67 (0.60, 0.75)	2	1.5 (1.3, 1.8)	0.84 (0.77, 0.92)	2
7		2.2 (1.7, 2.7)	0.69 (0.72, 0.65)	2	0.28 (0.16, 0.39)	0.95 (0.90, 1.00)	2
8		>110[c]	0.15 ± 0.06	4	2.7 ± 0.8[c]	0.38 ± 0.02	8
9					1.2 ± 0.6[a]	0.35 ± 0.08	3
10		>110[c]	0.08 ± 0.008	4	2.4 ± 1.7[c]	0.38 ± 0.05	4
11 (A-5,6-DTN)	H	38 ± 11	0.69 ± 0.043	8	4.4 ± 1.7	1.05 ± 0.08	7
12		1.70 ± 9.0	0.55 ± 0.03	4	21 (11, 30)	1.16 (0.91, 1.42)	2
13		0.16 (0.13, 0.18)	0.87 (0.85, 0.89)	2	0.25 (0.21, 0.28)	1.02 (0.93, 1.11)	2
14		1.8 (1.4, 2.2)	0.78 (0.72, 0.84)	2	0.73 (0.66, 0.80)	1.11 (1.00, 1.21)	2

[a] Relative intrinsic activity, calculated as maximal response to the compound divided by maximal response to isoproterenol. [b] Mean plus or minus standard error. [c] EC_{50} could not be reached, so EC_{20} is given. [d] Values for individual experiments where $n = 2$.

uent increased potency (compare **6** and **7**). Also, compounds possessing a phenylethyl substituent, e.g., **7**, were more potent than those with a phenylpropyl group, e.g., **9**. Within the aralkyl series there was a tendency for potency to be greatest for derivatives of A-5,6-DTN (compare **13** and **14** with **7** and **8**, respectively). The bis-A-6,7-DTN derivative, **10**, was only weakly active.

In the isolated left atria, most of the derivatives were capable of increasing force as much as isoproterenol, although, in general, the A-6,7-DTN derivatives possessed less intrinsic activity than those of A-5,6-DTN. This was also the case in the isolated right atrium, although in this tissue the intrinsic activity of most compounds was markedly less than that found in left atrium, regardless of the parent structure. Since the intrinsic activities were quite low in the right atrium, it was inappropriate to calculate an index of inotropic/chronotropic selectivity based on EC_{50} values. Therefore, inotropic selectivity and cardioselectivity were assessed in anesthetized dogs in a model previously designed for this purpose.[1,2]

In Vivo (Tables II and III). For comparative purposes, all in vivo data have been normalized to 50% [CF(50)] and 100% [CF(100)] increase in right ventricular contractile force. Inotropic selectivity was assessed by normalizing changes in heart rate to the CF(50) and CF(100) levels. Similarly, cardioselectivity was estimated by normalizing changes in diastolic blood pressure to the two levels of contractile force change. Experiments were also performed with dopamine, dobutamine, and isoproterenol.

The order of inotropic potency found in the dog was nearly equivalent to that obtained in the isolated cardiac tissue experiments. Thus, lowest activity was observed with the isopropyl derivatives **5** and **12** and with bis-A-6,7-DTN (**10**). Highest potency was obtained with derivatives possessing catechol substituents (**6**, **7**, **9**, and **13**), and, again, a methyl group on the carbon α to the amine, **7**, increased potency (compare **7** with **6**). In general, the derivatives of A-5,6-DTN had a greater potency than those of A-6,7-DTN.

The changes in diastolic blood pressure were marked and varied greatly throughout the series. All A-5,6-DTN derivatives possessed marked vasodepressor activity. Catechol derivatives of A-6,7-DTN possessing a methyl group on the α carbon of the amine substituent, **7** and **9**, also possessed strong vasodepressor actions. All other A-6,7-DTN derivatives possessed strong pressor activity.

The inotropic selectivity of most of the A-5,6-DTN and the A-6,7-DTN derivatives was significantly less than that

Table II. Inotropic Potency, Cardioselectivity, and Inotropic Selectivity of Aminoaralkyl Derivatives of A-5,6-DTN and A-6,7-DTN in Dogs

compound	N^a	potency, nmol/kg		cardioselectivity: Δ BP, mmHg		inotropic selectivity: Δ HR, bpm	
		CF(50)[b]	CF(100)[b]	CF(50)	CF(100)	CF(50)	CF(100)
1 (dopamine)	6	58.1 ± 6.9	125.0 ± 17.0	−15 ± 7	−5 ± 8	5 ± 5	12 ± 7
2 (dobutamine)	6	4.1 ± 0.5	13.2 ± 2.4	3 ± 1	4 ± 3	3 ± 1	17 ± 5
3 (isoproterenol)	6	0.11 ± 0.01	0.35 ± 0.10	−17 ± 2	−27 ± 2	13 ± 2	35 ± 12
4 (A-6,7-DTN)	5	173.0 ± 13.0	457.0 ± 134.0	29 ± 9	61 ± 10	−12 ± 9	21 ± 17
5	1	1560.0	[c]	46	[c]	9	[c]
6	6	85.1 ± 32.0	189.0 ± 77.0	50 ± 8	72 ± 10	11 ± 5	30 ± 6
7	6	11.4 ± 1.7	27.0 ± 3.6	−39 ± 4	−30 ± 5	−5 ± 5	4 ± 6
8	4	140.0 ± 8.0	410.0 ± 6.0	13 ± 15	60 ± 4	−3 ± 8	19 ± 2
9	5	24.6 ± 9.1	109.0 ± 47.0	−36 ± 9	−11 ± 21	20 ± 3	45 ± 7
10	2	961.0	2650.0	78	84	31	62
11 (A-5,6-DTN)	5	410.0 ± 90.0	[c]	41 ± 5	[c]	11 ± 6	[c]
12	1	110.0	[c]	−66	[c]	20	[c]
13	3	7.2 ± 5.4	20.1 ± 15.0	−42 ± 5	−54 ± 6	26 ± 9	40 ± 10
14	3	27.7 ± 10.8	196.0 ± 146.0	−51 ± 6	−61 ± 6	20 ± 6	41 ± 7

[a] N refers to number of experiments. [b] CF(50) and CF(100) refer to values obtained at 50 and 100% increase in right ventricular contractile force, respectively, as described under Experimental Section. Values are means ± SEM unless otherwise indicated. [c] Indicates the CF(100) levels were not obtained with the highest dose tested.

Table III. Effect of DMI[a] on the Inotropic Responses of A-6,7-DTN, A-5,6-DTN, and Dopamine

compd	dose, μg/kg, iv	N^b	% increase in contractile force: control	% increase in contractile force: DMI (1.0 mg/kg, iv)
4 (A-6,7-DTN)	50.0	6	59 ± 5	5 ± 5
11 (A-5,6-DTN)	200.0	3	57 ± 5	18 ± 4
12 (dopamine)	10.0	11	61 ± 8	13 ± 2

[a] Desmethylimipramine. [b] Number of experiments.

of dobutamine. In most cases, potency was also considerably less. However, two derivatives, 7 and 8, possessed excellent inotropic selectivity. The HR changes of compound 8 normalized to 50 and 100% increase in contractile force were of the same magnitude as those observed with dobutamine. The inotropic selectivity of 7 was significantly greater than that of dobutamine.

The unsubstituted parent compounds, 4 and 11, were found to possess a considerable degree of indirect sympathomimetic activity (Table III). Blockade of the amine uptake system of peripheral sympathetic nerve endings with desmethylimipramine caused a significant rightward shift in the inotropic dose–response relation for both A-5,6-DTN and A-6,7-DTN, as well as for dopamine.

Discussion

The effect of N-alkyl and N-aralkyl substitution on the cardiac activity of various catecholamines has been extensively investigated.[2,5-10] This is the first report, however, of aralkyl substitution of dihydroxyaminotetralin structures which do not contain a hydroxyl group in the position analogous to the β-hydroxyl group of phenethanolamine agents. Thus, the parent catecholamine structures of the present study (A-5,6-DTN and A-6,7-DTN) represent rigid forms of dopamine rather than norepinephrine. However, the present results are in general agreement with what is known about the effect of aralkyl substitution on catecholamine structures in general.

The present results indicate that, while the N-isopropyl derivatives of both types of ADTNs possess very weak activity at cardiac receptors, the aralkyl analogues of A-5,6-DTN were relatively more potent than those of A-6,7-DTN. This is in general agreement with the work of Ilhan[8] and Kohli[9] which indicated that the α rotamer of ADTN is preferred for β receptor activity. Furthermore, Kohli[9] has shown that the β rotameric form is more potent at the vascular α-adrenergic receptor. This was suggested in the present study also, since nearly all derivatives of A-6,7-DTN were strong vasopressor agents. However, two derivatives of A-6,7-DTN, 7 and 9, possessed potent vasodepressor properties. The receptor(s) responsible for this marked shift in activity, however, has not yet been identified.

Previous work has shown that 1-hydroxy-N-isopropyl-A-5,6-DTN possessed β-receptor activity equivalent in potency to isoproterenol.[10] This compound also appears to possess some degree of β_2 receptor selectivity. Furthermore, aralkyl derivatives of this catecholamine nucleus show even greater potency than isoproterenol, and β_2 selectivity is maintained.[5] Although we did not specifically identify the β_2 receptor as being responsible for the vasodepressor action of our A-5,6-DTN derivatives, the pattern of activity observed agrees with previous work. Thus, all A-5,6-DTN compounds possessed marked vasodepressor properties which were greater than that observed with isoproterenol. The potency of these compounds, however, was considerably less than that of isoproterenol, probably due to the lack of a hydroxy group in the 1 position. There was also a generalized increase in potency for contractile force when the amine was substituted with aralkyl functionalities, in agreement with previous work.[2,5,7]

Tuttle and Mills[2] have explored the effects of aralkyl substitution of dopamine on relative inotropic/chronotropic activity. Their results indicate that, in general, aralkyl substitution results in a relative decrease in chronotropic activity at any given level of inotropic effect. The most dramatic results were obtained with N-[3-(4-hydroxyphenyl)propyl] and N-[3-(4-hydroxyphenyl)-1-

(7) A. M. Lands and T. G. Brown, in "Drugs Affecting the Peripheral Nervous System", Vol. 1, A. Burger, Ed., Marcel Dekker, New York, 1967, Chapter 8, p 399.

(8) M. Ilhan, J. P. Long, and J. G. Cannon, *Arch. Int. Pharmacodyn. Ther.*, **223**, 215 (1976).

(9) J. D. Kohli, L. I. Goldberg, and D. E. Nichols, *Eur. J. Pharmacol.*, **56**, 39 (1979).

(10) Y. Oka, M. Motohashi, H. Sugihara, O. Miyashita, K. Itoh, M. Nishikawa, and S. Yurugi, *Chem. Pharm. Bull.*, **25**, 632 (1977).

methylpropyl] substituents. Incorporation of the latter group resulted in dobutamine, which is also a cardioselective compound with little activity at peripheral vascular β or α receptors. Within the present series of compounds there was no obvious tendency toward relative inotropic selectivity. In the 5,6-dihydroxy series, all compounds possessed marked chronotropic activity, including the compound which was substituted with the *N*-[3-(4-hydroxyphenyl)-1-methylpropyl] moiety of dobutamine, **14**. Thus, the effect of this group in imparting inotropic-selective properties when combined with dopamine cannot be extended to the A-5,6-DTN rigid form of dopamine. Compound **14** also possessed strong vasodepressor properties, indicating this substituent is also ineffective in imparting cardioselective properties when combined with A-5,6-DTN.

In the A-6,7-DTN series, only compounds **7** and **8** possessed any degree of inotropic selectivity. Compound **8** is the 6,7-dihydroxy semirigid analogue of dobutamine. It appeared, therefore, that the *N*-[3-(4-hydroxyphenyl)-1-methylpropyl] moiety is capable of imparting relative inotropic selectivity when combined with the 6,7-dihydroxy nucleus. However, the vasopressor action of the compound points to the ineffectiveness of this substituent in reducing peripheral vascular activity as is observed with dobutamine. In this regard, it appears that the pattern of peripheral vascular activity associated with the two types of ADTN nuclei predominate even when combined with this substituent, i.e., pressor with 6,7-dihydroxy and depressor with 5,6-dihydroxy. The activity of compounds **7** and **9** is somewhat of an anomaly both with respect to the 6,7-dihydroxy series and to each other. Both compounds were vasodepressors, but only **7** possessed excellent inotropic selectivity despite strong vasodepressor activity. Compound **9** showed no inotropic selectivity. Further experimentation is in progress aimed at identifying the receptor mechanisms responsible for the dramatically divergent results obtained with structural modifications in the 6,7-dihydroxy series.

Experimental Section

In Vitro Studies. Chronotropic and inotropic properties were assessed in vitro using spontaneously beating/electrically paced guinea pig right and left atria, respectively. Tissues were bathed in oxygenated (95% O_2–5% CO_2) Krebs–bicarbonate buffer containing 3.0×10^{-5} M EDTA. Loading tension was 0.5 g for right and 1.0 g for left atria. Right atria were studied at 37 °C and left atria at 30 °C. Left atria were paced at 1.5 Hz via field stimulation with silver electrodes in conjunction with a Grass S-44 stimulator and constant-current unit. Pacing was performed at current levels of 20% above threshold (4–8 mA). Pulse duration was 5 ms. Tissues were allowed to stabilize for 60 min after preparation and were washed periodically. In each experiment, an initial cumulative concentration–response curve (CCRC) was run with isoproterenol, and the tissues were washed. In right atria, a CCRC was then run with test compound. In left atria, the initial CCRC was discarded and another CCRC for isoproterenol was run, followed by washing. A CCRC was then run for test compound. EC_{50} values and relative intrinsic activities for the test compounds were calculated based upon maximal response obtained with isoproterenol.

In Vivo Studies. Mongrel dogs of either sex were anesthetized with pentobarbital sodium (30 mg/kg, iv, supplemented as needed) and ventilated through a cuffed endotracheal tube (Harvard, Model 613, 17 strokes/min, volume set by Harvard ventilation graph). Polyethylene catheters were placed in the left femoral artery and forelimb vein for measurement of arterial blood pressure (BP) and administration of drugs, respectively. The vagus nerves were severed in the cervical region, and body temperature was maintained with a heating pad. Heart rate (HR) was measured with a Beckman cardiotachometer triggered by the blood-pressure signal. A right thoracotomy was performed in the fifth intercostal space, and the right ventricle was exposed through a small (3 cm) pericardial incision. A precalibrated Walton–Brodie strain-gauge was attached with deep sutures to the right ventricular free wall, and the muscle beneath the gauge was stretched to 140% of its in situ length. HR, BP, and right ventricular contractile force (CF) were recorded on a Beckman recorder (R-611). After surgical preparation, a 30-min period was allowed for equilibration.

The inotropic/chronotropic and pressor/depressor activities of isoproterenol and test compounds were studied using bolus intravenous dosing. Catecholamine solutions were prepared daily using isotonic saline containing 0.5 mg/mL sodium bisulfite. A standard dose volume of 0.04 mL/kg was used for in vivo experiments. The peak response observed was used as an index of the effectiveness of each dose. Dose–response relations were established by increasing doses in 2-fold increments until a 100% increase in CF was obtained. A maximum of three different drugs was studied in any single experiment. The inotropic selectivity of all compounds was estimated by obtaining the HR change associated with 50 and 100% increase in CF. These normalized HR responses were obtained from inotropic and chronotropic dose–response curves by interpolation. Likewise, cardioselectivity was estimated by normalizing changes in BP to 50 and 100% increase in CF.[1,2] Normalized values were statistically compared using a *t* test and, when appropriate, a *t* test for paired observations. Preliminary experiments have indicated that autonomic reflexes have minimal influence on cardiac/pressor responses of isoproterenol and dobutamine in this experimental model. These results suggest, therefore, that the model is suitable for determining the cardiac/pressor actions of novel catecholamine structures (unpublished observations).

Chemistry. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 283 spectrophotometer as KBr pellets. NMR spectra were determined on a Varian T-60A spectrometer in $CDCl_3$ or CD_3OD using tetramethylsilane as a standard or D_2O using 4,4-dimethyl-4-silapentane-5-sulfonate as a standard. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

2-Amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (4). The compound was prepared using the method of Cannon[11] or Horn,[12] mp 268–270 °C (lit.[13] mp 270–271 °C).

2-Amino-5,6-dihydroxy-1,2,3,4-tetrahydronaphthalene (9). The compound was prepared using the method of Cannon:[11] mp >300 °C (lit.[14] mp >300 °C); NMR δ (D_2O) 1.5–2.5 (m, 4 H), 2.5–3.1 (m. 5 H), 3.1–3.8 (m, 1 H), 6.6–6.8 (m, 2 H).

General Method for the Reductive Amination of the ADTNs. Using the method of Borch,[4] a solution of 1 equiv each of 2-amino-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene or 2-amino-5,6-dimethoxy-1,2,3,4-tetrahydronaphthalene,[11,12] ketone or aldehyde, and sodium cyanoborohydride in methanol was stirred under a nitrogen atmosphere for 38 h. The methanol was removed in vacuo on a rotary evaporator, and the remaining solid was dissolved in water. The aqueous solution was extracted with ether. The combined extracts were dried ($MgSO_4$), dry hydrogen chloride was passed through the solution, and the resulting crystals were collected by filtration. Recrystallization was carried out in methanol/ether.

2-(Isopropylamino)-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (5). A mixture of 500 mg (2.05 mmol) of **4** dimethyl ether hydrochloride, 119 mg (2.05 mmol) of acetone, and 129 mg (2.05 mmol) of sodium cyanoborohydride in 20 mL of methanol under a nitrogen atmosphere was stirred for 48 h. An aqueous workup afforded **5** dimethyl ether. The crude product was dissolved in 40 mL of 48% hydrobromous acid, and the solution was heated to reflux under a nitrogen atmosphere for 24 h. The acid was removed in vacuo, the resulting solid was dissolved in water, cleared with Norit, and filtered, and the water was removed in

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vacuo, leaving 195 mg (31.5%) of light brown product: mp 125–126 °C; NMR (D_2O) δ 1.38 (d, J = 6 Hz, 6 H), 1.4–2.4 (m, 3 H), 2.5–4.8 (m, 7 H), 6.67 (s, 2 H). Anal. ($C_{13}H_{20}NO_2Br·0.5H_2O$) C, H, N.

2-(Isopropylamino)-5,6-dihydroxy-1,2,3,4-tetrahydronaphthalene (12). The compound was synthesized as for **5** in 65% yield: mp 211–213 °C; NMR (D_2O) δ 1.38 (d, J = 6 Hz, 6 H), 1.4–2.4 (m, 3 H), 2.5–4.8 (m, 7 H), 6.6–6.7 (m, 2 H). Anal. ($C_{13}H_{20}NO_2Br·H_2O$) C, H, N.

2-[[2-(3,4-Dihydroxyphenyl)ethyl]amino]-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (6). The reductive amination of the protected A-6,7-DTN and 3,4-dimethoxyphenyl glycidate[15] afforded MeO_4-**7** in 37% yield. Deblocking and workup as for **5** afforded **7** as an off-white solid: mp 183–185 °C; NMR (D_2O) δ 1.3–2.3 (m, 2 H), 2.3–3.0 (m, 6 H), 3.0–3.4 (m, 3 H), 6.3–6.9 (m, 5 H). Anal. ($C_{18}H_{22}NO_4Br·3H_2O$) C, H, N.

2-[[2-(3,4-Dihydroxyphenyl)-1-methylethyl]amino]-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (7). The reductive amination of the protected A-6,7-DTN and 3,4-dimethoxyphenylacetone (Aldrich) afforded a 35% yield of MeO_4-**7**. Deblocking and workup as for **5** afforded **7** as a dark solid: mp 145 °C; NMR (D_2O) δ 1.30 (d, J = 7 Hz), 1.5–2.3 (m, 2 H), 2.4–3.0 (m, 6 H), 3.3–3.9 (m, 2 H), 6.4–6.8 (m, 5 H). Anal. ($C_{19}H_{24}NO_4Br·1.5H_2O$) C, H, N.

2-[[3-(4-Hydroxyphenyl)-1-methylpropyl]amino]-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (8). The reductive amination of the protected A-6,7-DTN and 4-(*p*-hydroxyphenyl)-2-butanone (Aldrich) afforded MeO_2-**8** in 90% yield. Deblocking and workup as for **5** afforded **8** as an off-white powder: mp 236–237 °C; NMR (CD_3OD) δ 1.3–1.7 (m, 3 H), 1.7–3.8 (m, 12 H), 6.43 (s, 2 H), 6.65 (d, J = 7 Hz, 2 H), 7.00 (d, J = 7 Hz, 2 H). Anal. ($C_{20}H_{26}NO_3Br$) C, H, N.

2-[[3-(2,4-Dihydroxyphenyl)-1-methylpropyl]amino]-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (9). The reductive amination of the protected A-6,7-dTN and 4-(3,4-dimethoxyphenyl)-2-butanone[16] afforded MeO_4-**9** in 60% yield. Deblocking and workup as for **5** afforded **9** as a pale brown solid: mp 199–201 °C dec; NMR (CD_3OD) δ 1.40 (d, J = 6 Hz, 3 H), 1.6–2.4 (m, 4 H), 2.4–3.0 (m, 6 H), 3.0–3.7 (m, 2 H), 4.8 (6 s, 9 H), 6.3–6.8 (m, 5 H). Anal. ($C_{20}H_{26}NO_4Br·H_2O$) C, H, N.

2,2'-Iminobis[1,2,3,4-tetrahydro-6,7-naphthalenediol] (10). The reductive amination of the protected A-6,7-DTN and 3,4-dimethoxy-2-tetralone[11,12] afforded MeO_4-**7**·HCl in 90% yield. The dicatechol proved to be too unstable to afford a correct combustion analysis, so a correct C, H, N analysis was obtained on MeO_4-**10**·HCl: NMR (CD_3OD) δ 1.7–2.6 (m, 4 H), 2.7–3.2 (m, 8 H), 3.2–3.8 (m, 2 H), 3.77 (s, 12 H), 6.55 (2, 4 H). Deblocking and workup as for **5** afforded **10** as a pale brown solid: mp 244–246 °C; NMR (CD_3OD) δ 1.4–2.4 (m, 4 H), 2.6–3.2 (m, 8 H), 3.3–4.0 (m, 2 H), 6.47 (s, 4 H).

2-[[2-(3,4-Dihydroxyphenyl)-1-methylethyl]amino]-5,6-dihydroxy-1,2,3,4-tetrahydronaphthalene (13). The reductive amination of the protected A-5,6-DTN and 3,4-dimethoxyphenylacetone (Aldrich) afforded a 37% yield of MeO_4-**13**. Deblocking and workup as for **5** afforded **13** as a yellow solid: mp 160–161 °C; NMR (D_2O) δ 1.35 (d, J = 7 Hz, 3 H), 1.8–2.4 (m, 2 H), 2.4–3.1 (m, 6 H), 3.3–3.8 (m, 2 H), 6.3–6.9 (m, 5 H). Anal. ($C_{19}H_{24.33}NO_4Br_{1.33}·3H_2O$) C, H, N, Br.

2-[[3-(4-Hydroxyphenyl)-1-methylpropyl]amino]-5,6-dihydroxy-1,2,3,4-tetrahydronaphthalene (14). The reductive amination of the protected A-5,6-DTN and 4-(*p*-hydroxyphenyl)-2-butanone (Aldrich) afforded MeO_2-**14** in 86% yield. Deblocking and workup as for **5** afforded **14** as an off-white solid: mp 241–242 °C; NMR (D_2O) δ 1.43 (d, J = 7 Hz, 3 H), 1.5–2.4 (m, 4 H), 2.5–3.1 (m, 6 H), 3.1–3.8 (m, 2 H), 6.4–7.3 (m, 6 H). Anal. ($C_{20}H_{26}NO_3Br·H_2O$) C, H, N.

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Synthesis and Biological Evaluation of the Methyl Esters of (+)-12-Fluoro-13,14-dihydroprostaglandin $F_{2\alpha}$ and (+)-15-*epi*-12-Fluoro-13,14-dihydroprostaglandin $F_{2\alpha}$

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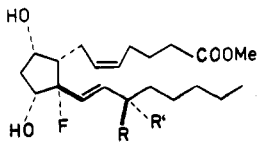
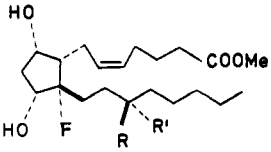
(+)-12-Fluoro-13,14-dihydroprostaglandin $F_{2\alpha}$ methyl ester (**2a**) and (+)-15-*epi*-12-fluoro-13,14-dihydroprostaglandin $F_{2\alpha}$ methyl ester (**2b**) were prepared from the readily available (−)-7-fluorospiro[bicyclo[2.2.1]hept-5-ene-2,2'-[1,3]dioxolane]-7-methanol (**3**). Fluoroprostaglandins **2a** and **2b** possess truly significant separations of antifertility activity from smooth-muscle stimulating properties. In addition, our studies showed that **2a** and **2b** were totally inert toward the placental 15-hydroxyprostaglandin dehydrogenase.

The luteolytic effect associated with prostaglandin $F_{2\alpha}$ which enables man to control the reproductive cycle of animals[1] prompted us some years ago to synthesize novel fluoroprostaglandins in hopes of developing analogues of natural $PGF_{2\alpha}$ which possess enhanced luteolytic potency while being devoid of smooth-muscle stimulating activity. Our demonstration[2] that both (+)-12-fluoro$PGF_{2\alpha}$ methyl ester (**1a**) and (+)-15-*epi*-12-fluoro$PGF_{2\alpha}$ methyl ester (**1b**)



1a R = H, R' = OH
1b R = OH, R = H



2a R = H, R' = OH
2b R = OH, R' = H

possess significant activity in the hamster antifertility assay while exhibiting lowered smooth-muscle stimulating properties (see Table I), coupled with similar observations by Andersen[3] with (+)-13,14-dihydro$PGF_{2\alpha}$ methyl ester

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